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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,575	SCHENK, DALE B.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,58 and 74-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,58 and 74-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/31/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks and amendments filed 31 July 2006 have been entered. Claims 11, 58, and 74 – 81 are pending and under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections

3. The following rejections made in the previous office action are withdrawn:

A. The objections to the claims are withdrawn in light of the amendments.

B. The rejections under 35 USC § 103 are withdrawn in light of the amendments and arguments. The claims now require peripheral administration of antibodies to NAC for treatment of disease. Applicant argues that the prior art teaches away from the invention, as the reference by Masliah specifically teaches that antibodies to NAC should not be administered *in vivo* for treatment of neurological diseases as they will not cross the BBB (see p. 41 final paragraph). Applicant's arguments are persuasive; the prior art teaches away from the invention now claimed.

Maintained Rejections and Objections

Priority

4. The effective filing date for all claims is 1 June 1999 for the reasons of record.

Claim Rejections - 35 USC § 112

5. Claims 11, 58, and 74 – 81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of administering antibodies which bind to the NAC fragment of synuclein and antibodies which bind to an epitope within residues 1 – 28 of Abeta, does not reasonably provide enablement for therapeutic or prophylactic treatment of Alzheimer's disease as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In previous office actions, the examiner had indicated that the claims were not enabled as there were no working examples of therapeutic treatment by administration of antibodies that bind to the NAC fragment of synuclein. After considering applicant's arguments and careful

consideration of the claimed invention, the examiner now agrees that since the specification provides evidence of some degree of enablement of treatment by administration of antibodies that bind to an epitope with residues 1-28 of Abeta. Specifically, beginning on p. 95 the specification describes an experiment in which several antibodies were administered to mice for 196 days. Mice treated with PBS had significantly higher total Abeta in the cortex than mice treated with polyclonal antibodies (p. 99). PBS-treated mice had more Abeta 1-42 in the hippocampus than mice treated with antibody 10D5, which binds to residues 1-12. The differences approached, but did not reach statistical significance (p. 101). Furthermore the specification discloses that the antibodies against Abeta can cross the blood brain barrier in an amount sufficient to decrease the levels of Abeta, as the antibodies were detectable in the CNS of both wild-type and transgenic mice (see paragraph bridging pp. 104 – 105). The totality of the evidence suggests that antibodies which bind to an epitope within residues 1-28 of Abeta will decrease the amount of Abeta in the brain when administered peripherally.

The claims require administration of both antibodies to Abeta and those to NAC. There is no evidence that the therapeutic effects of the anti-Abeta antibodies will be neutralized by co-administration with anti-NAC antibodies. If anything, the art teaches that these antibodies may not be as effective as other proteins as they may be at least partially excluded by the blood-brain barrier (see Masliah et al., WO 95/06407, of record, p. 41, final paragraph). Thus the examiner concedes that co-administration will have at least some therapeutic effect, namely reduction of the amount of Abeta in the brain, and the specification provides doses of antibodies used. However, the specification does not provide enablement for "therapeutically treating" as broadly claimed and does not provide enablement for "prophylactically treating" as broadly claimed.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

In the instant case the nature of the invention, therapeutically or prophylactically treating Alzheimer's disease, is complex. The art recognizes that the disease has many features,

including short-term memory loss, behavioral abnormalities, as well as a multitude of anatomical abnormalities such as the presence of both amyloid plaques and neurofibrillary tangles. See for example Small et al. 2000. Proc Natl Acad Sci USA 97:6037-6042, cited in the office action mailed 17 October 2005. Additionally, Alzheimer's disease is characterized by changes in permeability of the blood brain barrier; see Anderson (U.S. Patent 5,589,154), particularly column 6 lines 27 – 40, where the reference teaches that beta-amyloid protein, the causative agent in Alzheimer's diseases, also induces vascular damage.

The art also recognizes that treatment of the disease is essentially impossible, although there are therapies which ameliorate certain symptoms of Alzheimer's. See Anderson, column 3, lines 56 – 60. The specification provides working examples of treatment of a mouse model of Alzheimer's, called the PDAPP transgenic mouse, by administering antibodies. This mouse recapitulates some, but not all of the features of the human disease. The specification discloses that PDAPP mice have increased Abeta plaque deposition in comparison to wild-type mice, and that treatment with anti-Abeta antibodies results in decreased Abeta in the brains of the PDAPP mice. Post-filing references indicate that treatment of these mice with anti-Abeta antibodies improves a measure of spatial memory (see Hartman et al., 2005. Journal of Neuroscience 25:6213-6220, especially Figure 5) long-term potentiation, a cellular model of memory (see Hartman, Figure 7). Furthermore, treatment with anti-Abeta antibodies also improves acetylcholine release (see Bales 2006. Journal of Clinical Investigation 116:825-832). These are consistent with the assertion in the specification that treatment includes partial arrest of the symptoms of the disease (see specification, p. 51, second paragraph). Thus the specification is enabling for decreasing the severity of the learning deficits and concentration of Abeta within the brain, and for attenuating the decrease in acetylcholine release by administration of antibodies which bind to Abeta.

However, the specification is not enabling for treatment, either therapeutic or prophylactic, as defined in the specification. The definition of the treatments appears at p. 51 of the specification and is reproduced below:

E. Treatment Regimens

In prophylactic applications, pharmaceutical compositions or medicaments are administered to a patient susceptible to, or otherwise at risk of, a particular disease in an amount sufficient to eliminate or reduce the risk or delay the outset of the disease. In therapeutic applications, compositions or medicants are administered to a patient suspected of, or already suffering from such a disease in an amount sufficient to cure, or at least partially arrest, the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as a therapeutically- or pharmaceutically-effective dose. In both prophylactic and therapeutic regimes, agents are usually administered in several dosages until a sufficient immune response has been achieved. Typically, the immune response is monitored and repeated dosages are given if the immune response starts to wane.

Clearly, the definition of therapeutic treatment includes curing of Alzheimer's disease. The definition of to cure includes the reversal of symptoms and restoration to health (see Merriam-Webster online medical dictionary, entry for "cure", accessed 5 September 2006). Alzheimer's disease is characterized by death of cholinergic neurons. In order to cure the disease, which is included within applicant's definition of therapeutic treatment, the therapy would have to reanimate dead neurons. This is not shown in the specification, and the art recognized that it was impossible. Similarly, the specification defines a prophylactic treatment to include one that eliminates the risk of coming down with the disease. While the specification discloses that treatment with anti-Abeta antibodies delays the onset of the formation of plaques, it does not disclose prevention of all symptoms. Thus while it is enabling for delaying the "outset [onset?] of the disease", which appears within the definition of prophylactic treatment on p. 51, the specification does not disclose complete prevention. Thus the specification is not enabling for prophylactic treatment as defined.

Claim Rejections - 35 USC § 103

6. Claims 11, 58, 74 – 75 and 78 – 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masliah (WO 95/06407, published 9 March 1995, of record), in view of Becker (EP 0 613 007, published 18 February 1994, cited on IDS filed 11 December 2001), and Solomon (1996. Proc Natl Acad Sci USA 452-455, of record).

This rejection is maintained for the reasons of record. Briefly, Masliah teaches treatment of Alzheimer's disease by administration of an "NAC/NACP polypeptide", which is defined to include antibodies which bind to the NAC fragment of synuclein and specifically includes those

antibodies recited in claims 11, 58, 74-75, and 78-79. However Masliah does not teach antibodies which bind to an epitope within residues 1 – 28 of A-beta.

Becker teaches administration of antibodies which bind to A-beta for treatment of Alzheimer's disease (see column 7 lines 44 – 52). Becker's antibodies include fragments of antibodies such as Fab and Fab', as well as chimeric and humanized antibodies (see column 5 lines 50 – 58). However Becker does not teach the specific epitope to which the antibodies bind, nor does Becker teach antibodies which bind to NAC.

Solomon teaches that monoclonal antibodies which bind to residues 8 – 17 and 1 – 28, which are named 6F/3D and AMY-33 respectively, are able to inhibit aggregation of A-beta into its toxic aggregated forms. However Solomon does not teach administration of antibodies to patients.

It would have been obvious to one of ordinary skill in the art to co-administer antibodies which bind to the NAC component of alpha-synuclein, as taught by Masliah, and antibodies which bind to an epitope within residues 1 – 28 of A-beta, for treatment and prophylaxis of Alzheimer's disease, with a reasonable expectation of success. The motivation to do so would be to treat Alzheimer's disease.

Applicant argues that as the claims have been amended to recite the new limitation of peripheral administration, the invention is non-obvious with respect to the prior art. Specifically, applicant argues that the reference by Masliah teaches away from peripheral administration of antibodies for treatment of disease. Applicant refers to pp. 5 and 41 of the Masliah reference for support.

Applicant's arguments have been fully considered but they are not persuasive. The Masliah reference does not in fact teach away from administration of antibodies. On p. 41, the reference states that "[b]ecause of the blood/brain barrier, it can be expected that antibodies will not be particularly the preferred reagant [*sic*] for use in *in vivo* applications." This does not constitute a teaching away from the administration of antibodies peripherally. Rather, the sentence merely indicates that one might not expect the antibodies to be the ideal compound to be administered. The disclosure of multiple embodiments of varying degrees of efficacy does not teach away from administration of any one of the embodiments. There is no evidence of record that administration of antibodies will not be successful. In fact, quite to the contrary, Becker teaches that antibodies are to be administered to treat Alzheimer's disease. In contrast to applicant's argument that one would not have an expectation of success in treating

Alzheimer's disease by peripherally administering antibodies, Becker teaches that this is to be done and specifically points out the peripheral routes of administration that the artisan is to use (see for example Becker, column 7 lines 39 – 52 and column 8 lines 25 – 42). Thus the artisan would have a reasonable expectation of success in administering the antibodies peripherally for treatment of disease. The invention now claimed remains obvious, as it is obvious to co-administer two compositions known to be effective for the same purpose.

Applicant also argues, on p. 7 of the remarks, that Becker does not identify which epitopes antibodies that bind A-beta should be directed to. Applicant's arguments have been fully considered but they are not persuasive. While Becker does not teach the specific residues, Becker does teach that the antibodies should be those that bind to beta sheets, and Solomon teaches that antibodies which bind to residues 8 – 17 and 1 – 28 are able to inhibit aggregation of A-beta into its toxic aggregated forms, thereby guiding the artisan to select these specific antibodies in the administration protocols of Becker.

7. Claims 11, 58, 74 – 75, 77 - 79 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masliah in view of Becker, and Solomon as applied to claims 11, 58, 74 – 75, and 78 – 79 above, and further in view of Sabel (U.S. Patent 4,883,666, issued 28 November 1989).

Applicant did not traverse this rejection but rather argued that the parent claims are non-obvious. As the examiner has determined the parent claims are obvious over the prior art, this rejection stands for the reasons of record.

Conclusion

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DK

Daniel E. Kolker, Ph.D.
September 13, 2006

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER